REMARKS

The Office Action dated May 1, 2006, and the follow-up assertion of a non-compliant amendment, dated March 29, 2007, have been carefully considered. Since the issues underpinning the assertion of noncompliance pervasively effected the substantive content of the Amendment, the entire allegedly non-compliant Amendment is hereby replaced with this present Amendment. This Amendment, taken with the accompanying Remarks, is believed sufficient to overcome the objections and rejections and establish the patentability of the claims, thereby placing the present application in condition of allowance. Reconsideration and an early allowance are therefore respectfully requested. According to the present amendment, claim 1 has been amended to expound on the inventive methods by including teachings found, for example, on page 11, lines 6-16. New claim 9 has been added to capture the embodiment disclosed, e.g. on page 8, lines 17-19, whereby anaerobic *P. aeruginosa* biofilms reveal upregulated expression of OprF, and new claim 10 has been added to capture the embodiment whereby presence of OprF is indirectly confirmed by a finding of antibodies to OprF, disclosed, for example, on page 11, lines 20-24. As it is believed the amendment does not involve the addition of new matter, entry and consideration are in order and are respectfully requested.

Claims 1-10 are currently pending and claims 1, 2 and 9-10 are subject to examination.

Noncompliance

The Amendment of November 1, 2006 was asserted as non-compliant due to the insertion of language into the sole independent claim which appeared to change the nature of the claim from a method of assessing as per the elected invention, to a method of treating, as per the withdrawn election. Applicants dispute this interpretation, and note that the confusion underscores Applicant's original traversal of the restriction requirement on the basis that these embodiments are directed to a single invention. However, in order to expedite prosecution, Applicant's have amended the claims to eliminate references to treatment regimens. However, this excision of language necessitates a re-writing of the remarks section accordingly. The present Amendment is believed to be in full compliance with 37 CFR 1.142(b) such that entry and consideration on the merits are respectfully requested.

Objection to the Drawings

The drawings are objected to on the basis that "reproductions of gels are of such poor quality they were unreadable." Preliminarily, Applicants note that this language provides very sparse guidance as to the basis of the objection and therefore how to obviate it, and does not refer specifically to which of the drawings it is intended to apply. Nonetheless, Applicants addressed Figure 4 because it specifically illustrates gels, and amended the drawing so that resolution is sufficient for the observer to discern the differences being illustrated. Applicants believe this corrects the objection as asserted and that the objection is therefore overcome.

35 U.S.C. § 112, Enablement

Claims 1-2 are rejected under 35 U.S.C. § 112, first paragraph, assertedly because the specification, "while being enabling for methods of detecting a *Pseudomonas aeruginosa* infection by the detection of its porin F protein (OprF), does not reasonably provide enablement for methods for assessing cystic fibrosis disease based on the presence or absence of any outer membrane protein generally, or OprF specifically. The Examiner asserts, inter alia, that the claims encompass all out membrane proteins of any cell type or organism. This rejection is traversed and reconsideration is respectfully requested.

Independent claim 1, as presently amended, is directed to a method for Cystic Fibrosis (CF) disease assessment in an individual, the method comprising: (a) detecting the presence or absence of a *Pseudomonas aeruginosa* outer membrane protein (OprF) in a sample from an individual, (b) making a determination of whether a mucous lining in an airway of the individual is substantially anaerobic, and (c) assessing the disease state of the individual accordingly.

Applicants submit that the amendment to insert the identity of the particular infective agent, *Pseudomonas aeruginosa,* into this claim as the modifier/source of the OprF sufficiently restricts the breadth of the claim to what is enabled by the present specification, and as set forth by the Examiner.

Hence, the rejection of claims 1 and 2 under 35 U.S.C. § 112 for lack of enablement has been overcome. Reconsideration is therefore respectfully requested.

35 U.S.C. § 112, Written Description

Claims 1-2 are rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Specifically the Examiner asserts that the claims are drawn to methods of assessing C disease by detecting the presence or absence of outer membrane protein in a sample where "assessing" is defined according to the specification to include a number of activities, and that the instant claims therefore claim "all outer membrane proteins of any cell type or organism whereas the specification only discloses the prevalence of *Pseudomonas aeruginosa* infections among CF patients," and "fails to describe any other outer membrane protein that is either directly or indirectly associated with CF." This rejection is traversed and reconsideration is respectfully requested.

As presently amended, independent claim 1 is directed to a method for Cystic Fibrosis (CF) disease assessment in an individual, the method comprising: (a) detecting the presence or absence of a *Pseudomonas aeruginosa* outer membrane protein (OprF) in a sample from an individual, and (b) making a determination of whether a mucous lining in an airway of the individual is substantially anaerobic.

Applicants submit that, as amended, the language makes it clear that the outer membrane protein recited in the claims is the porin protein F of a *Pseudomonas aeruginosa* pathogen. The omission of this source modifier from the original claim was inadvertent. Hence, the basis for the Examiner's assertion of lack of written description has been obviated and the rejection of claims 1 and 2 under 35 U.S.C. § 112 for lack of written description has been overcome. Reconsideration is respectfully requested.

35 U.S.C. § 112, Indefiniteness

Claims 1 and 2 were further rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner asserts that claim 1 is rendered vague and indefinite by the parenthetical use of the term "OprF" because it is unclear whether this term is meant to be an abbreviation for outer membrane proteins

generally or is referring to the porin F protein of *Pseudomonas aeruginosa*. This rejection is traversed and reconsideration is respectfully requested.

Instant independent claim 1, as presently amended, is set forth in detail above. Applicants submit that the instant claim, as amended, makes it clear that the term "OprF" refers to the porin F protein of the pathogen, *Pseudomonas aeruginosa*, and that the scope of the claim is commensurate with this limitation.

Hence, the rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph has been overcome and reconsideration is respectfully requested.

35 U.S.C. § 102

Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Mutharia et al *Infection and Immunity,* 1983, Vol. 42 No. 3, pages 1027-1033 (hereafter "Mutharia"). Specifically, the Examiner asserts that Mutharia discloses measuring OprF in *Pseudomonas aeruginosa* isolates from CF patients. This rejection is traversed and reconsideration is respectfully requested.

Instant claim 1, as amended, is directed to a method for Cystic Fibrosis (CF) disease assessment in an individual, the method comprising: (a) detecting the presence or absence of a *Pseudomonas aeruginosa* outer membrane protein (OprF) in a sample from an individual, (b) making a determination of whether a mucous lining in an airway of the individual is substantially anaerobic, and assessing the disease of the individual accordingly.

Mutharia, on the other hand, is concerned with characteristics of protein F in outer membranes isolated from numerous serotypes and CF-derived clinical isolates of *P. aeruginosa*, including localization of antigenic sites on the protein F (see Abstract, and page 1027, last paragraph, bridging to page 1028). Mutharia reports on the production of six monoclonal antibodies specific for porin protein F of *P. aeruginosa* (see Discussion, page 1031, first paragraph), and teaches that a main observation of the study was the determination that protein F is surface exposed and accessible to antibodies (id., second full paragraph). Mutharia discloses the use of monoclonal antibodies "as sensitive

immunological probes in the study of the surface properties of the bacteria, and specifically, the surface localization of protein F on intact cells.

There is no teaching in Mutharia of a method for CF disease assessment in an individual. The only mention of CF patients in Mutharia is as a source for several of the clinical isolates of *Pseudomonas aeruginosa* pathogen. While it is clear from the Mutharia discussion that OprF was derived from some of these pathogens, there is no teaching in Mutharia of the significance of this to determining the presence of anaerobic *Pseudomonas aeruginosa*, and determining whether or not the mucous of the airway lining of an individual subject provide anaerobic or aerobic conditions to pathogens. Such a determination is important, as presently disclosed, in deciding appropriate treatment regiments, as certain antibiotics are differentially effective according to this factor.

Indeed, Applicants submit that Mutharia fails to consider any OprF implications related to CF disease assessment, and fails to disclose any steps which may be construed as methods for assessing CF disease.

Applicants submit that the most that Mutharia may be asserted for, is the recognition that chronic CF patients are a source for *Pseudomonas aeruginosa*, and that OprF is a *Pseudomonas aeruginosa* membrane protein. Mutharia further discloses various structural characteristics of membrane protein F, but that disclosure is inapposite to the asserted rejection basis or the patentability of instant independent claim 1.

Anticipation under 35 U.S.C. § 102(b) requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). Mutharia fails to disclose methods for CF disease assessment in an individual. In particular, Mutharia fails to disclose a recognition that OprF detection indicates presence of highly problematic anaerobic conditions, and the need to tailor treatment regimens accordingly. Mutheria fails to disclose methods comprising detecting the presence or absence of OprF, determining whether the mucous lining of the airways is substantially anaerobic, and assessing the disease accordingly.

Hence, the rejection of claim 1 as being anticipated by Mutharia has been overcome and reconsideration is respectfully requested.

35 U.S.C. § 103

Claims 1-2 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mutharia. Specifically the Examiner asserts that Mutharia discloses measuring OprF in *Pseudomonas aeruginosa* isolates from CF patients, but differs from the instant invention in that Mutharia does not explicitly disclose the direct testing of surface liquid, sputa, or combinations thereof. The Examiner asserts, however, that since Mutharia discloses that OprF levels can be detected in *Pseudomonas aeruginosa* from CF patients, it would have been obvious for one of ordinary skill in the art to use the detection of OprF in biological samples to determine whether a given CF patient had a *Pseudomonas aeruginosa* infection, with a reasonable expectation of success since Mutharia discloses that OprF was present on *Pseudomonas aeruginosa* from CF patients. This rejection is traversed and reconsideration is respectfully requested.

Independent claim 1 is set forth in detail, above.

Applicants do not dispute either than *Pseudomonas aeruginosa* is known to be detectable in some CF diseased patients, or that OprF is known to be a membrane protein of *Pseudomonas aeruginosa*. Neither the present inventors nor Mutharia are the originators of these discoveries. However, the present inventors realized that OprF is expressed variably over the course of CF disease, and that at the point where it is detected in the secretions of a CF patient, anaerobic conditions have developed in the mucous linings of the airways of the patient such that CF disease is assessed. This assessment is a crucial preliminary step to providing an appropriate and effective treatement regimen, as antiobiotics are known to be differentially selective based on the presence of anaerobic or aerobic conditions, as presently taught.

Mutharia neither teaches nor discloses methods related to the assessment of CF disease, and the disclosure by Mutharia of the presence of OprF on the surface of the pathogen is not suggestive of methods of CF disease assessment. Mutharia fails to disclose the significance of this detection in a patient, or assessing and thereafter adapting treatment regimens according to the assessment. Mutharia is concerned with the structural

characteristics of the surface of OprF, not the underlying significance of its presence or absence in a CF patient.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Furthermore, references relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979). Dependent claims are nonobvious under §103 if the independent claims from which they depend are nonobvious. *In re Fine,* 837 F.2d 1071, 5 USPQ 2d 1596 (Fed. Cir. 1988). Mutharia merely teaches the sampling of some OprF from CF patient-derived *Pseudomonas aeruginosa* in the course of their study of surface characteristics of over 20 OprF samples from various sources. There is no teaching or suggestion of the significance of the detection of OprF in a CF diseased patient, or any steps which may be construed as a method for CF disease assessment in an individual based on that detection. Hence, a prima facie case of obviousness is not established on the basis of Mutharia.

Further, mere recognition that a pathogen is present in a disease state, or that a protein is present on a pathogen, in the absence of a recognition of any significance to this with respect to that disease state, does not enable methods, such as the currently inventive methods, for assessing the disease state. The teachings of Mutharia therefore neither render the present invention obvious, nor enable it.

Hence, instant independent claim 1, and claim 2 dependent therefrom, are nonobvious and patentable over Mutharia. The rejection under 35 U.S.C. §103 is therefore overcome and reconsideration is respectfully requested.

It is believed that the above is a complete and comprehensive response to the rejections of claims 1-2 under 35 U.S.C. §§ 112, first and second paragraphs, 102, and 103, as asserted in the May 1, 2006 Office Action, and overcomes the reasons for the Examiner's assertion that the Amendment dated November 1, 2006 is noncompliant. Reconsideration and an early allowance are respectfully requested. In order to expedite prosecution of this

application and to promote efficiency, the Examiner is invited to contact Applicants at the contact below to discuss any remaining unresolved issues.

Respectfully submitted,

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